REMARKS/ARGUMENTS

In response to the Notice of Non-Compliant Amendment mailed October 22, 2007, the claim listing has been revised to include a listing of all of the claims. After entry of this amendment, claims 56-58, 61, 63-66, 71-79, 81, 83, 85, 86, 92-94, 97, 99, 101-191, 194-205, and 207-209 are pending and under consideration.

Claim 57 has been amended in accordance with the Examiner's suggestion as discussed below. The Examiner's remarks are addressed using the paragraph numbering of the office action. The amendment should not be construed as acquiescence in any ground of rejection. In some instances, the rejections have been addressed without comment on certain matters raised by the Examiner not relevant to the basis for response to the rejection. Any such lack of comments should not be construed as acquiescence in the Examiner's position.

¶4. For purposes of responding to the present office action, applicants accept the Examiner's determination of priority. Applicants reserve the right to show an earlier date of invention should it be relevant is this or other proceeding.

¶9. Claim 57 has been amended as suggested.

¶¶10-11. Claims 57 and 184 stand rejected for alleged lack of enablement on the basis that the 266 antibody is not particularly effective for removal of Aβ from the brain. The Examiner also cites Solomon (1998) as evidencing variability of performance between different antibodies in maintaining solubility of Aβ and that the 266 antibody exhibited only a low effect in this assay.

Initially, applicant notes that an inference based on the data in the specification that the 266 antibody is "not particularly effective" is insufficient to fulfill the Examiner's burden of showing lack of enablement. *CFMT, Inc. v. Yieldup Int'l Corp,* 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003), discussed in more detail in the appeal brief, held that any meaningful "cleaning" would satisfy the claimed goal of "cleaning of semiconductor wafers."

By analogy any meaningful pharmacological activity of the 266 antibody would be sufficient to satisfy the enablement requirement in the present claims.

In any event, irrespective of any reservations the Examiner may have regarding the data in the specification, pharmacological activity of the 266 antibody has been confirmed by post filing evidence. For example, Dodart et al., Nature Neuroscience 5, 452-457 (2002) (*see* cite no. 595 of the supplemental IDS filed December 15, 2005 report that the 266 antibody was effective in reversing cognitive defects in a transgenic mouse model of Alzheimer's disease. Similarly US Patent Publication No. 20060153772 (a copy of which is submitted herewith) reports 266 improved memory using a different transgenic mouse model of Alzheimer's disease (*see* paragraph 291). It is noted that Dodart proposes that the reversal of cognitive defects was effected by a mechanism independent of amyloid burden. However, practice of the present claims is not dependent on an understanding of mechanism. Thus, practice of the presently claimed methods or use of the claimed compositions in such methods inherently results in a therapeutic or prophylactic activity irrespective whether that activity is achieved through reduction in plaque burden or otherwise.

Solomon (1998)'s results indicating the 266 antibody performed poorly in an *in vitro* solubilization assay may illustrate the limited capacity of this *in vitro* assay to predict *in vivo* activity but do not detract from the *in vivo* results later obtained. Bard's results indicating that certain antibodies are ineffective in reducing amyloid burden do not mean that such antibodies cannot be effective by other mechanisms, such as that discussed by Dodart.

In the aggregate, the evidence indicates that the 266 antibody does have a pharmacological activity useful in treatment and prophylaxis of Alzheimer's disease. Accordingly, it is respectfully submitted that the rejection should be withdrawn.

¶¶12-14. Claims 56, 58, 61-66, 71-73, 77-79, 86, 97, 183, 185-191, 194-196, 200-202 and 205 stand rejected as allegedly anticipated by Solomon, US 5,688,651, as evidenced by Fox, Fukutani and Pluckthun. Solomon is alleged to teach an antibody AMY-33 binding to an epitope formed by residues 25-28 of Aβ for use in treating Alzheimer's disease. Solomon is also alleged to teach via incorporation by reference of Pluckthun engineered antibodies that include single

chain antibodies, antibody fragments, bispecific antibodies and humanized antibodies. The Examiner also alleges that although Solomon is silent as to pharmaceutical compositions, a skilled person would reasonably have expected that an antibody would have been contained within a pharmaceutically acceptable composition. This rejection is respectfully traversed.

It is respectfully submitted that creation of purportedly novel combinations between Solomon's disclosure Pluckthun's disclosure is impermissible. Essential subject matter can only be incorporated by reference to a US patent or published application. Other sources of material can only be used for nonessential subject matter (*i.e.*, subject matter referred to for purposes of indicating the background of the invention or illustrating the state of the art) (MPEP § 608.01(p)). Here, Pluckthun is not a US patent or published application, and so can be incorporated by reference only to illustrate background of the invention or illustrate the state of the art. Hence, combining Pluckthun's disclosure with that of Solomon to give rise to novel combinations not present in either reference or other art goes beyond using the incorporated reference to illustrate the background or state of the art. At least for this reason, Solomon does not disclose chimeric or humanized forms of an AMY-33 antibody.

Furthermore, the assumption underlying the rejection that the AMY-33 antibody discussed by Solomon binds to an epitope within residues 25-28 of Aβ has been determined to be incorrect. This epitope, which is characterized as putative by Solomon based on AMY-33 being raised against a 1-28 fragment of Aβ, and Yankner et al., Science 250:279-282 (1990) (a copy of which is submitted herewith) having speculated that residues 25-35 of Aβ mediated toxic effects. The putative epitope 25-28 represents the intersection of the fragment generating AMY-33 with the 25-35 toxic region hypothesized by Yankner et al. Applicant submits herewith a declaration by Dr. Peter Seubert, who attempted to determine the epitope specificity of AMY-33 experimentally. In brief, Dr. Seubert found that AMY-33 did not bind to an epitope within residues 13-28 Aβ. Thus, Solomon's hypothesis regarding AMY-33 binding to an epitope within residues f 25-28 of Aβ is incorrect.

For these reasons, it is respectfully submitted that the Examiner has not established that Solomon discloses any antibody binding to an epitope within residues 13-28 of Aβ much less a humanized, chimeric or human antibody binding to such an epitope.

The Examiner also cited Fox and Fukutani but did not provide any explanation why either reference was cited. In any event, it is respectfully submitted that neither reveals an inherent property of Solomon that would compensate for the above-noted deficiencies.

¶¶15-16. Claims 97, 99 and 164-182 stand rejected as obvious over Anderson and Becker in view of Schenk. Anderson and Becker are alleged to teach methods of diagnosing amyloid plaques in individuals using an antibody to Aβ. Schenk is alleged to teach that antibodies specific for residues 13-28 are useful for detecting of Aβ because they are not cross-reactive with the larger amyloid precursor protein. Schenk is also alleged to teach methods for *in vivo* diagnosis and treatment of Aβ related conditions. The Examiner takes the view that it would have been obvious to combine the 13-28 epitope specificity disclosed by Schenk in *in vivo* methods of diagnosis for the benefit of distinguishing between Aβ and APP. This rejection is respectfully traversed.

Although Schenk refer to *in vivo* detection of Aβ, the contemplated detection is of Aβ in patient fluid samples, such as blood or the CSF, and that the detection is performed on samples of such fluids by ELISA or similar assays. The term "*in vivo*" is used to distinguish such assays on body fluids, from assays of Aβ in cell culture media, which are characterized as being *in vitro* assays. (*See* col. 6, lines 1-15). Schenk does not disclosure detection of detecting amyloid plaques by imaging *in vivo*. Further, as was discussed at length in the appeal brief, Schenk disclosure of therapeutic methods relates to "small molecules, biological polymers, such as polypeptides, polysaccharides, polynucleotides, and the like" rather than antibodies. The 266 antibody and other antibodies to Aβ are mentioned in the context of assays for detection of Aβ peptide in screening methods to identify such compounds (*see* cols. 8 and 9, and particularly col. 14, lines 13-27).

It is respectfully submitted that the artisan would not have found it obvious to make a chimeric, humanized or human antibody binding to an epitope within residues 13-28 for use *in vivo* imaging in a patient, not least because the 266 antibody has little if any propensity to bind to amyloid plaques that form the principal pathology of Alzheimer's disease. The lack of ability of the 266 antibody to bind aggregated Aβ is discussed in the present application at p. 70,

lines 19-20 and in DeMattos et al., PNAS 98, 8850-8855 (2001) at p. 8854, second column, first paragraph of cite no. 469 of the supplemental IDS filed July 30, 2004. In Schenk, the 266 antibodies was used to detect Aβ by *in vitro* ELISA assay (irrespective whether the source of Aβ was *in vivo* body fluid samples or *in vitro* culture media assays). In such assays, the Aβ can be detected in soluble form, and the specificity of the 266 antibody for the soluble form is not a problem. However, if one were interested in detecting amyloid pathology in a living subject, lack of binding of an antibody to amyloid deposits would be a major concern that would almost certainly end any efforts to develop a chimeric or humanized version of the 266 antibody of Schenk for such a purpose.

At least for this reason, it is respectfully submitted that it would not have been obvious to make a humanized, chimeric or human antibody binding to an epitope within residues 13-28 of Aβ for detecting amyloid plaques in a subject.

¶17. Claims 74-76, 81, 85, 92, 197-199, 203-204 and 207 stand rejected as allegedly obvious over Solomon as evidenced by Fox in view of Becker or Adair. Solomon is cited as allegedly teaching the antibody AMY-33 which recognizes an epitope within residues 13-28 of Aβ and residues 25-28 in particular. Becker and Adair are cited as allegedly teaching benefits of humanized antibodies to reduce immunogenicity. Adair is also cited as allegedly teaching use of the human IgG1 isotype in humanized antibodies. The Examiner alleges that it would have been obvious to combine the references for the benefit of reduced immunogenicity and that Solomon's report that the AMY-33 antibody was effective in preventing Aβ aggregation *in vitro* would have provided a reasonable expectation of success. This rejection is respectfully traversed.

The rejection is premised on the AMY-33 antibody binding to an epitope within residues 13-28 of Aβ, which is turn is based on Solomon's hypothesis that AMY-33 binds to an epitope formed by residues 25-28 of Aβ. As discussed in Dr. Seubert's declaration, this hypothesis is incorrect. AMY-33 does not bind to an epitope within residues 13-28 of Aβ .

In addition, applicant disagrees that it would have been obvious to combine Adair's discussion of the human IgG1 isotype with Becker or Solomon. Adair indicates that the human IgG1 or IgG3 are preferred "when antibody effector functions are required" (at p. 6, line

58). However, Adair does not provide any indication that effector functions would be desired for *in vivo* detection of amyloid deposits in Alzheimer's patients. To the contrary, the skilled person would likely have thought that effector functions were undesirable in view of the belief that Alzheimer's disease was at least in part an inflammatory disease. These concerns are expressed in an article in the Washington Post appearing shortly after the present inventor's work in clearing plaques by immunization with Aβ was first published.

> The idea was revolutionary because most Alzheimer's experts believe that the inflammation provoked by amyloid plaques contributes to the destruction of brain cells. Many predicted that stirring up the immune system with a vaccine would only make the disease worse. . .Schenk's 1999 papers on the Elan vaccine created a sensation not least because the unexpected findings suggested that vaccines might be helpful in disorders where no one had thought of using them. His results have since been confirmed by other researchers.
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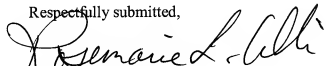
> Washington Post, May 8, 2001 (submitted herewith).

The belief that stirring up the immune system would only make the disease worse would have suggested that effector functions would be undesirable. Absent any indication that effector functions would be desirable for treatment or prophylaxis of Alzheimer's disease, it would not have been obvious to combine Adair's discussion of human IgG1 with Becker or Solomon.

¶18. Claims 93-94 and 208-209 stand rejected as allegedly obvious over Solomon in view of Becker and Adair in further view of Williams. Williams is alleged to teach repeated dosing or administration of a sustained released composition. In reply, it is respectfully submitted that claims 93-94 and 208-209 would have been nonobvious for at least the same reasons as the independent claims from which they depend.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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